## REMARKS

### I. Introduction

This paper is submitted in response to the Office action mailed August 2, 2005. A three-month extension of time for response is respectfully requested. Claims 1-34 and 36-60 are pending in the present application. Claims 1-34 and 36-60 have been rejected.

The Examiner has noted that the originally filed Declaration recites the wrong provisional application number, *i.e.*, 60/008,317 rather than correctly reciting application number 60/008,717. Applicants enclose a new Declaration executed by the inventors that correctly references provisional application 60/008,717 to correct this inadvertent error.

### II. The Rejections Under 35 U.S.C. §112 ¶1 Should Be Withdrawn

The Examiner has rejected claims 1-30, 36-47 and 50-52 under 35 U.S.C. 112 ¶1, alleging that the specification enables producing chimeric RNA in a cell *in vitro*, but does not enable the *in vivo* production of a chimeric RNA for therapeutic treatment in a cell. In particular, the Examiner alleges that at the time the invention was made efficient *in vivo* delivery and expression of foreign DNA in a cell could not be achieved by any method.

The present invention is directed to a modified synthetic nucleic acid molecule (claims 1-33, 50-53); a composition comprising a physiological acceptable carrier and a nucleic acid molecule (claim 34); an expression vector comprising an RNA polymerase promoter and a nucleic acid molecule (claims 36-47); a method for synthesizing the nucleic acid molecule (claims 48-49); and a method of producing a chimeric RNA molecule in a cell (claims 54-60). Thus, claims 1-34 and 36-53 do not require delivery

and expression of foreign DNA. Accordingly, for at least these reasons, reconsideration and withdrawal of the rejection with regard to these claims is respectfully requested.

Regarding therapeutic use of the claimed nucleic acid molecules in a cell, it is alleged that the specification does not reasonably provide enablement for use *in vivo*. In particular, the Examiner argues that the application does not show a correlation between *in vitro* trans-splicing and the production of *in vivo* therapeutic effects. Applicants respectfully point out that only claims 54-60 are directed to a method of producing a chimeric RNA molecule in a cell.

Applicants respectfully submit that the *in vitro* models disclosed in specification provide sufficient evidence of *in vivo* efficacy of the present invention. (*See* MPEP 2164.02). As acknowledged by the Examiner, the mechanism of spliceosome-mediated trans-splicing is the same whether it occurs *in vivo* or *in vitro*. The specification discloses the successful transfer of PTMs into cells and accurate replacement of an internal exon by a double-trans-splicing between a target pre-mRNA and a PTM RNA containing both 3' and 5' splice sites leading to production of a full length functionally active protein. In addition, Applicants have previously published working examples of *in vivo* trans-splicing to produce a chimeric RNA using the same methods disclosed in the present invention. *See* Puttaraju *et al.*, *Spliceosome-mediated RNA trans-splicing as a Tool for Gene Therapy*, Nature Biotechnology, vol. 17, 246-52 (1999) ("Puttaraju *et al.*"). Accordingly, Puttaraju *et al.* proves that the *in vitro* models disclosed in the present specification correlate with the results obtained *in vivo*. Thus, the *in vitro* models disclosed in the specification constitutes a working example, sufficient to support enablement of the claimed nucleic acids and cells *in vivo*. For at least these reasons,

Applicants respectfully submit that the disclosure of the present invention would enable the production of a chimeric RNA in a cell *in vivo*.

In view of the foregoing, and Applicants response filed May 24, 2005, reconsideration and withdrawal of the rejection of claims 1-30, 36-47 and 50-52 under 35 U.S.C. 112 ¶1 is respectfully requested.

## III. The Double Patenting Rejections Should be Withdrawn

Claims 1-33, 36-47 and 50-60 have been rejected under the judicially created doctrine of obviousness-type double patenting in view of: claims 1-27 of U.S. Patent No. 6,083,702. Claims 1-34, 36-47 and 50-60 have been rejected under the judicially created doctrine of obviousness-type double patenting in view of: claims 1-6, 9-18 and 28-32 of U.S. Patent No. 6,280,978; claims 1-51 of U.S. Patent Application No. 09/756,096; claims 1-23, 28-35 and 37-39 of U.S. Patent Application No. 09/941,492; claims 1-6, 9-23 and 28-34 of U.S. Patent Application No. 09/838,858; and claims 1-8, 10-21 and 23-39 of U.S. Patent Application No. 10/456,153.

Applicants file herewith a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) to overcome the rejection based on the judicially created doctrine of double patenting, to disclaim the terminal part of the statutory term of any patent granted on the above-identified application, which would extend beyond the expiration date of U.S. Patent No. 6,083,702 and U.S. Patent No. 6,280,978. In addition, the terminal disclaimer disclaims the terminal part of the statutory term of any patent granted on the above-identified application, which would extend beyond the expiration date of any patent granted from U.S. Patent Application No. 09/756,096, U.S. Patent Application No.

09/941,492, U.S. Patent Application No. 09/838,858 and U.S. Patent Application No. 10/456,153.

Therefore, in view of the foregoing, reconsideration and withdrawal of the rejection is respectfully requested.

## IV. Conclusion

In view of the foregoing remarks reconsideration and allowance of the pending claims is respectfully requested.

A three-month extension of time for response is respectfully requested. Payment of the extension fee and terminal disclaimer fee are to be made according to the Credit Card Payment Form attached herewith. Applicants believe that no additional fees are required in connection with this response. However, if additional fees are required, the Commissioner is hereby authorized to charge any additional payment, or credit any overpayment, to Deposit Account No. 01-2300, **referencing Docket Number 027705.00004.**

Respectfully submitted,

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**FEE CALCULATION**

Any additional fee required has been calculated as follows:

X If checked, "Small Entity" status is claimed.

| | (Column 1) | (Column 2) | (Column 3) | SMALL ENTITY | | | LARGE ENTITY | |
|---|---|---|---|---|---|---|---|---|
| | CLAIMS REMAINING AFTER AMENDMENT | HIGHEST NO. PREVIOUSLY PAID FOR | PRESENT EXTRA | RATE | ADD'L FEE | OR | RATE | ADD'L FEE |
| TOTAL CLAIMS | 145 MINUS | 158 | = -0- | x $25 | $0.00 | | x $50 | $ |
| INDEP CLAIMS | 12 MINUS | 12 | = -0- | x $100 | $0.00 | | x $200 | $ |
| ☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM | | | | + $180 | $PAID | OR | + $360 | $ |
| | | | | | $0.00 | | | $ |

The U.S. Patent and Trademark Office is hereby authorized to charge and deficiency or credit any overpayment of fees associated with this communication to Deposit Account No. **01-2300** referencing docket number **027705.00004**.